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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 149 PCT	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/EP2004/050375	International filing date *(day/month/year)* 26.03.2004	Priority date *(day/month/year)* 28.03.2003
International Patent Classification (IPC) or national classification and IPC C07K16/24, A61K39/395, A61K39/385, A61K39/00, A61P37/02, A61P11/00, A61P37/08		
Applicant INNOGENETICS N.V. et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

Date of submission of the demand	Date of completion of this report
19.10.2004	25.02.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Lechner, O Telephone No. +49 89 2399-8687

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/050375

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-45 as originally filed

Claims, Numbers

1-16 as originally filed

Drawings, Sheets

1/1 as originally filed

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-8, 10-16 (in part)

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 1-8, 10-16 (in part) are so unclear that no meaningful opinion could be formed *(specify)*:

see separate sheet

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	5-7, 10-16
	No:	Claims	1-4, 8, 9
Inventive step (IS)	Yes:	Claims	
	No:	Claims	5-7, 10-16
Industrial applicability (IA)	Yes:	Claims	1-16
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

item III

1. Major Clarity problems (Article 6, PCT)

1. **Claims 1** and **2** do not meet the requirements of **Article 6, PCT** in that the matter for which protection is sought is not clearly defined. The claims attempt to define the subject-matter by reference to a desirable characteristic or property, namely, IFN-gamma neutralizing molecule. This sole indications, however, do not allow the skilled person to understand which compound(s) fall within the scope of the claims. Thus, the claims lack clarity in the sense of **Article 6, PCT**. This lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.

2. **Claims 1, 3-8** and **10-16** are not acceptable under **Article 6, PCT**. The therapeutic application is functionally defined by a pathophysiological mechanism, i.e. T1 inflammatory lung disease, which does not allow any defined therapeutic application in the form of a real treatment of a pathological condition (disease).

The objection could be overcome by introducing in the claims a list of pathological conditions (diseases) cited in **claim 2**.

3. Consequently, the examination of novelty and inventive step has been carried out for those parts of the above cited claims which appear to be clear in the sense of **Article 6, PCT**, i.e. the use of anti-IFN-gamma Ab (c.f. **claim 3**) for treating the diseases listed e.g. in **claim 2**.

item V

1 Reference is made to the following documents:

D1 DENIS M ET AL: 'MURINE HYPERSENSITIVITY PNEUMONITIS BIDIRECTIONAL ROLE OF INTERFERON-GAMMA' CLINICAL AND EXPERIMENTAL ALLERGY, vol. 22, no. 8, 1992, pages 783-792, XP002257503 ISSN: 0954-7894

D2 WO 01 34180 A (ZIESCHE ROLF ;BLOCK LUTZ HENNING (DE)) 17 May 2001 (2001-05- 17)

D3 WO 02 069996 A (LOVELACE RESPIRATORY RES INST ;TESFAIGZI YOHANNES (US)) 12 September 2002 (2002-09-12)

D4 BEERS-MH AND BERKOW-R (EDS): 'The merck manual of diagnosis and therapy' 1999 , MERCK RESEARCH LABORATORIES; page 628, XP002257638

2 Novelty (Article 33(2), PCT)

2.1 D1 discloses that treatment with anti-IFN-gamma Ab results in diminished lung

fibrotic response in mice treated with F. rectivirgula, a model for experimental hypersensitivity pneumonitis (HP). Accordingly, HP designates a group of diseases which are determined by the inhalation of antigens such as Farmer's lung and pigeon breeders' lung. HP can also be modulated positively by direct exogenous IFN-gamma. The authors also argue, that the results are consistent with the results obtained in other mouse models and in human subjects with Farmer's lung (c.f. abstract, page 790, lhc, §2; page 784, lhc; page 789, lhc, §2).
D1 relates to the treatment of HP (e.g. Farmer's lung) a T1 inflammatory disease. According to **D4,** bronchiolitis occurs to some degree in about 50% of patients with farmer's lung - i.e. **D1** intrinsically also discloses a method to prevent bronchiolitis. In view of the teachings of **D1** (vide supra) the subject matter of **claims 1-3, 4** and **8-9**, as far as examined (c.f. item III above) does not appear to be novel in the sense of **Article 33(2), PCT**.

2.2 **D2** describes the use of interferon-gamma for treating asthma e.g. severe asthma (c.f. page 2; claims 1, 2)
D3 describes the use of interferon-gamma for treating asthma e.g. severe asthma, chronic bronchitis or cystic fibrosis (abstract; page 1, line 26 - page 2, line 13; page 4, line 23-26; page 5, line 1-11; page 7, line 4-6; page 11, line 22-30).
Thus, on the basis of **D2** and **D3**, respectively, the subject matter of **claims 8-10**, as far as examined (c.f. item III above) does not appear to be novel in the sense of **Article 33(2), PCT**..

2.3 The subject matter found in **claims 5-7** and **10-16**, as far as examined (c.f. item III above), would appear to be novel in the sense of **Article 33(2), PCT**.

3 Inventive step (Article 33(3), PCT)

D1 is considered to be the closest prior art and discloses that treatment with anti-IFN-gamma Ab results in diminished lung fibrotic response in mice treated with F. rectivirgula, a model for experimental hypersensitivity pneumonitis (HP). Accordingly, HP designates a group of diseases which are determined by the inhalation of antigens. Two important forms of the disease are Farmer's lung and pigeon breeders' lung. HP can also be modulated positively by direct exogenous IFN-gamma. The authors also argue, that the results are consistent with the results obtained in other mouse models and in human subjects with Farmer's lung.

3.1 The subject matter of **claim 5-7, 10-14, 15-16**, as far as examined (c.f. item III above), differs from document **D1** (vide supra) in that it describes IFN-gamma neutralizing strategies for preventing or treating the specific T1 inflammatory lung

diseases COPD, emphysema, chronic bronchitis, severe asthma, sarcoidosis, berylliosis, cystic fibrosis.
The technical problem of the present application is to provide medications to treat specific T1-inflammatory lung diseases.
The claimed solution is the use of an anti-IFN-gamma Ab (**claims 5-7**), immunogenic IFN-gamma (**claims 10-14**) and APCs loaded with IFN-gamma (**claims 15, 16**).

From the teachings of the closest prior art alone it would be obvious for the skilled person that he could try to neutralize the action of IFN-gamma e.g. by application or induction of specific human anti-IFN-gamma Ab using well known methods in order to prevent/treat also different other T1 inflammatory (lung) diseases.

Therefore, the subject matter of **claims 5-7** and **10-16** would not appear to involve an inventive step in the sense of **Article 33(3), PCT**.

item VII

1 The applicant should also erase general statements which imply that the extent of protection may be expanded in some vague and not precisely defined way such as on page 10, §2; page 11, line 6 (see **PCT Guidelines, Section IV, C-III, 4.3a)**
2 Contrary to the requirements of **Rule 5.1(a)(ii), PCT**, the relevant background art disclosed in **D1**, appears not to be mentioned/discussed in the description, nor is this document identified therein.

item VIII

1 In a later European regional phase objections might be raised against any expression within the description such as "...incorporated by reference..." (e.g. on page 10, §2) as the regional patent law requires that the application is self-contained.
2 Abbreviations used within the claims should be spelled out at first occurrence, and then introduced by placing the abbreviation in parentheses after the term being abbreviated (e.g. COPD) (**Article 6, PCT**).